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1 **Continuous attractor network models of grid cell firing based on**
2 **excitatory-inhibitory interactions**

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16
17 *Keywords:* Gamma oscillation, recurrent network, neural computation,
18 excitation, inhibition, epilepsy

19
20
21 **Key points summary:**

22
23 1. Neurons with grid firing fields are thought to encode estimates of location
24 computed from self-motion signals.

25
26 2. Evidence points towards continuous attractor networks as a substrate for
27 grid firing, but the cellular mechanisms are not well understood.

28
29 3. Computational models of excitatory and inhibitory cells with realistic
30 membrane dynamics account for grid firing and related network oscillations.

31
32 4. We argue that investigation of predictions from models of this kind will be
33 essential to establish mechanisms for grid firing and other cognitive
34 computations.

37 **Abstract**

38 Neurons in the medial entorhinal cortex encode location through spatial firing
39 fields that have a grid-like organisation. The challenge of identifying
40 mechanisms for grid firing has been addressed through experimental and
41 theoretical investigations of medial entorhinal circuits. Here, we discuss
42 evidence for continuous attractor network models that account for grid firing
43 by synaptic interactions between excitatory and inhibitory cells. These models
44 assume that grid-like firing patterns are the result of computation of location
45 from velocity inputs, with additional spatial input required to oppose drift in the
46 attractor state. We focus on properties of continuous attractor networks that
47 are revealed by explicitly considering excitatory and inhibitory neurons, their
48 connectivity and their membrane potential dynamics. Models at this level of
49 detail can account for theta-nested gamma oscillations as well as grid firing,
50 predict spatial firing of interneurons as well as excitatory cells, show how
51 gamma oscillations can be modulated independently from spatial
52 computations, reveal critical roles for neuronal noise, and demonstrate that
53 only a subset of excitatory cells in a network need have grid-like firing fields.
54 Evaluating experimental data against predictions from detailed network
55 models will be important for establishing the mechanisms mediating grid firing.

56

57

58 **Abbreviations:** MEC, medial entorhinal cortex; L2SCs, layer 2 stellate cells;
59 L2PCs, layer 2 pyramidal cells; E-I, excitatory-inhibitory; PV, parvalbumin.

60

61 **Introduction**

62 Neural representations of space within the hippocampus and medial
63 entorhinal cortex (MEC) are critical for navigation and memory. Grid cells in
64 the MEC have firing fields that encode position using an allocentric, regular
65 triangular matrix or *grid*-like firing pattern (Hafting et al., 2005). Grid
66 representations have the properties of a high capacity, high resolution and
67 error correcting code for self-localisation (Fiete et al., 2008; Mathis et al.,
68 2012; Sreenivasan and Fiete, 2011). The spatially periodic features of grid
69 firing fields have led to the view that they are the output of computation by a
70 path integrator that translates self-motion signals into estimates of location
71 (McNaughton et al., 2006). In this review, we will consider evidence that
72 network attractor dynamics arising from excitatory-inhibitory interactions
73 account for grid firing patterns within MEC circuits.

74

75 The organisation within the MEC of spatial firing properties is an important
76 constraint on mechanistic models for grid firing. Grid cells form networks in
77 anatomically overlapping but functionally discrete modules, with cells of the
78 same module sharing their grid spacing and orientation but having randomly
79 distributed phases (relative offset of grid apices) (Barry et al., 2007; Hafting et
80 al., 2005; Stensola et al., 2012). The highest density of grid cells is in layer 2
81 of the MEC (Sargolini et al., 2006). Grid cells in this layer also show the
82 greatest prospective bias in their code for location (Kropff et al., 2015). There
83 are two major populations of excitatory cells in this layer. Neurons positive for
84 the marker reelin have stellate morphology and project to the dentate gyrus of
85 the hippocampus (Klink and Alonso, 1997; Varga et al., 2010), while neurons
86 positive for calbindin have a more pyramidal morphology and project to the
87 CA1 region of the hippocampus (Kitamura et al., 2014; Ray et al., 2014;
88 Varga et al., 2010). We will refer to these cell populations as layer 2 stellate
89 cells (L2SCs) and layer 2 pyramidal cells (L2PCs) respectively (Klink and
90 Alonso, 1997)(L2SCs and L2PCs have also been referred to as 'Ocean' and
91 'Island' cells (Kitamura et al., 2014)). Both L2SCs and L2PCs may have grid
92 firing fields, although the majority of neurons in each population do not appear
93 to generate typical grid firing patterns (Sun et al., 2015; Tang et al., 2014).
94 During behaviours that produce grid firing, neurons in superficial layers of the

MEC also generate fast gamma frequency (60-140 Hz) oscillations that are modulated by the slower theta rhythm (Chrobak and Buzsaki, 1998; Colgin et al., 2009). While all grid cells encode location through their firing rate, some also represent location through timing of their action potentials relative to the network theta rhythm (Hafting et al., 2008; Reifenshtein et al., 2012).

Several conceptual models have been proposed to explain grid firing patterns (for reviews see (Burgess and O'Keefe, 2011; Giocomo et al., 2011; Zilli, 2012)). However, implementing models in ways that are consistent with the biophysics and connectivity of entorhinal neurons is challenging (Pastoll et al., 2012; Remme et al., 2010). Here, we will explore insights from models in which grid-like firing patterns emerge as a result of path integration in continuous attractor networks composed of excitatory and inhibitory neurons, with membrane potential dynamics that approximate real neurons (Figure 1). We will argue that this class of models is particularly useful as they can be constrained by experimentally measured synaptic connectivity and oscillatory network activity, as well as by action potential firing during spatial behaviours. They therefore generate specific predictions that are testable by diverse experimental approaches from anatomical analysis through to electrophysiological recordings of single cell and network activity.

Continuous attractors networks as models for grid generation

Continuous attractor networks are dynamical systems whose intrinsic properties drive activity towards a stable state; this can be visualised in a state space comprising an energy surface upon which stable states are represented by low energy regions (Brody et al., 2003). States existing outwith these regions will decay 'downwards' towards the low energy points. A network's intrinsic connections can be configured so its preferred states will correspond to localised bumps of activity. Mathematical functions can then be implemented in the network's state space by movement of the bumps of activity in response to inputs to the network (Conklin and Eliasmith, 2005; Eliasmith, 2005). In continuous attractor network models of spatial coding, the

127 computation performed is integration of velocity input to generate an estimate
128 of location relative to a known start point, referred to as path integration
129 (McNaughton et al., 1996; McNaughton et al., 2006; Samsonovich and
130 McNaughton, 1997; Zhang, 1996). Such networks do not necessarily
131 generate triangular grid-like firing fields, but can do so with appropriately
132 configured connections. In networks that model grid firing, stable states
133 manifest either as a bump (Figure 2A) or as multiple bumps of activity (Figure
134 2B) on a two-dimensional sheet of phase-arranged grid cells (Fuhs and
135 Touretzky, 2006; Guanella et al., 2007). Given velocity inputs the activity
136 bump(s) represent movement in space by propagating across the sheet. This
137 mechanism for path integration can be implemented by networks in which
138 individual grid cells receive velocity inputs tuned to a particular movement
139 direction, with the local connections of each grid cell offset so that an increase
140 in its input will tend to push the activity bump in an appropriate direction
141 across the neural sheet (Burak and Fiete, 2009; Fuhs and Touretzky, 2006;
142 Guanella et al., 2007). Alternatively, path integration could be achieved
143 through interactions between a layer of heading-independent grid cells and
144 multiple layers of head direction-modulated grid cells, which each integrate a
145 single head direction input with speed signals and feedback from the heading-
146 independent grid layer (Samsonovich and McNaughton, 1997). While the
147 latter class of models require many more neurons to account for path
148 integration, because separate layers are required for each heading direction,
149 they have the advantage that they naturally account for direction modulated
150 (or conjunctive) grid cells as well as pure grid cells.

151
152 Continuous attractor network models have been implemented at various
153 levels of detail and a close correspondence to known neural connectivity or
154 dynamics is not necessary to generate grid-like firing fields. Indeed,
155 experimental observations have corroborated a number of generic predictions
156 that are independent of the details of the circuitry used for model
157 implementation (McNaughton et al., 2006). 1. Populations of grid cells are
158 organised into modules in which each neuron has a common spatial phase
159 and orientation (Stensola et al., 2012). 2. The spatial phase relationship
160 between cells is maintained even following environmental manipulations that

161 restructure the spatial firing pattern of individual cells (Yoon et al., 2013). 3.
162 The envelope of the membrane potential of grid cells changes slowly on entry
163 to and exit from their firing fields (Domnisoru et al., 2013; Schmidt-Hieber and
164 Hausser, 2013). 4. Removal of excitatory drive causes cells that previously
165 had grid fields to encode head direction (Bonnevie et al., 2013), which is
166 consistent with movement of activity bumps in continuous attractor networks
167 relying on each grid cell receiving a tuned head direction input (Bonnevie et
168 al., 2013; Burak and Fiete, 2009; Fuhs and Touretzky, 2006; Guanella et al.,
169 2007; Pastoll et al., 2013).

170

171 While these observations are consistent with continuous attractor network
172 models accounting for rate coded grid fields, most existing models do not
173 readily account for precession in the timing of action potentials fired by some
174 grid cells relative to the theta rhythm (Hafting et al., 2008; Reifenstein et al.,
175 2012). One-dimensional attractor networks, based on interaction between a
176 direction-independent cell population and direction modulated cell
177 populations, can generate repeating firing fields and phase precession
178 (Navratilova et al., 2012). Extension of this mechanism to two dimensions will
179 require additional neuronal layers for each heading direction (Samsonovich
180 and McNaughton, 1997). An alternative is that phase precession and attractor
181 states are established independently. For example, phase precession can be
182 explained by hybrid models that include a mechanism for grid firing based on
183 interference between oscillations (Burgess et al., 2007; Hasselmo et al.,
184 2007), in addition to mechanisms for generation of network attractor states
185 (Bush and Burgess, 2014; Schmidt-Hieber and Hausser, 2013).

186

187 **Emergence of attractor states through excitatory-inhibitory interactions**

188 How might attractor mechanisms for grid firing be implemented in networks of
189 neurons? Do the properties of neural circuitry in the MEC constrain models or
190 lead to predictions that distinguish between different models? Grid
191 computation in continuous attractor networks requires emergence of stable
192 bumps of activity. This can be achieved using reduced models in which
193 separate populations of excitatory and inhibitory neurons are not explicitly
194 considered. In these models, either each neuron locally excites nearby

195 neurons and inhibits more distant neurons (Fuhs and Touretzky, 2006), or
196 spatially structured inhibitory connections act in concert with excitatory drive
197 to the whole network (Burak and Fiete, 2009; Couey et al., 2013). However,
198 use of local excitatory connections is inconsistent with evidence that L2SCs
199 are not directly connected to one another (Dhillon and Jones, 2000; Pastoll et
200 al., 2013; Couey et al., 2013), but instead interact indirectly via inhibitory
201 interneurons (Pastoll et al., 2013; Couey et al., 2013). Moreover, because grid
202 cells are excitatory neurons, an inhibitory output from grid cells is inevitably an
203 over-simplification. One could address this by assuming that the inhibitory
204 output from grid cells is equivalent to an excitatory connection to a dedicated
205 inhibitory interneuron. However, this is inconsistent with convergent (many to
206 one) and divergent (one to many) connectivity between excitatory and
207 inhibitory networks (Couey et al., 2013), and with there being many more
208 excitatory than inhibitory neurons in layer 2 of the MEC (Canto et al. 2008).
209 Thus, while offering conceptually important explanations for grid firing,
210 reduced models are limited in their ability to evaluate consequences of
211 experimentally determined connectivity.

212
213 Models that explicitly consider interactions between separate populations of
214 excitatory and inhibitory neurons inevitably differ from reduced models,
215 leading to new insights and predictions (Pastoll et al., 2013; Solanka et al.,
216 2015; Widloski and Fiete, 2014). Given appropriately structured network
217 connectivity these excitatory-inhibitory (E-I) models generate network attractor
218 states (Figure 2). Structured connectivity can be implemented by varying the
219 strength of connections between neurons according to their position in the
220 network, while maintaining a fixed probability of a connection being present
221 (Pastoll et al., 2013; Solanka et al., 2015; Widloski and Fiete, 2014).
222 Alternatively, synaptic strength can remain fixed but the probability of
223 connections varied as a function of distance between pre- and postsynaptic
224 neurons on the neural sheet (Solanka et al., 2015). Evidence that the
225 amplitude of inhibitory inputs to stellate cells has a bimodal distribution is
226 consistent with structuring of connection probability rather than the strength of
227 connections (Couey et al 2013). Models based on E-I interactions also
228 demonstrate that velocity inputs, which are required for movement-dependent

translation of their activity bumps, may target either interneurons or excitatory cells (Pastoll et al. 2013). While spatial firing of cells with inhibitory output is implicit in reduced models, in E-I models interneurons have spatial firing fields that depend on the wiring of the network. For example, either surround inhibition or surround excitation supports grid firing by excitatory cells, but in the latter case interneurons have inverted grid fields, whereas in the former they have grid-like fields (Pastoll et al. 2013).

Two important recent experimental studies introduce challenges beyond simply accounting for grid firing by excitatory cells. First, while the firing fields of parvalbumin (PV) positive interneurons have significant spatial stability, they typically have grid scores below the threshold for grid firing, only rarely appear to have a clear grid like organisation (Buetfering et al. 2014), and on visual inspection also do not appear to have inverted firing fields although this is difficult to establish quantitatively. Second, when layer 2 cells are imaged in freely moving animals, only about 10 % of identified L2SCs and L2PCs have grid-like firing fields (Sun et al., 2015). This is surprising given that neurons within each population appear to have similar synaptic connectivity and intrinsic properties. This could suggest that the grid firing neurons correspond to sub-groups of cells with distinct, but not yet identified, cellular or circuit properties. Otherwise, models for grid firing must explain how grid patterns are produced by only a subset of neurons that at a cellular and circuit level are indistinguishable from non-grid cells.

These challenges may be addressed using E-I networks and by considering that in vivo entorhinal neurons may receive spatial signals that can be considered as noise in the sense that they are not used to promote grid firing. Thus, when E-I models are extended to include random spatial input to interneurons, excitatory neurons in these networks continue to generate grid-like firing fields, but the hexagonal symmetry of interneuron firing fields is reduced (Figure 3)(Solanka et al. 2015). In these networks the fraction of excitatory and inhibitory cells classified as grid cells drops substantially, with almost no interneurons classified as having grid fields (Figure 3). Thus, the finding that only a subset of layer 2 cells have grid-like firing fields need not

263 imply that grid and non-grid cells are distinguished by distinct cellular or circuit
264 properties, while the absence of a clear grid signature in the firing of individual
265 interneurons may nevertheless be compatible with models based on E-I
266 interactions.

267

268 **Single and multi-bump networks differ in their local and long-range** 269 **connectivity**

270 Continuous attractor network models for grid firing exist in versions that differ
271 in their number of activity bumps. These functional differences result primarily
272 from connections spanning different distances relative to the size of the
273 network.

274

275 In single bump networks (also referred to as periodic networks, cf. Widlowski
276 and Fiete, 2015) the planar attractor manifold is wrapped into a torus
277 (Guanella et al., 2007; Pastoll et al., 2013; Samsonovich and McNaughton,
278 1997). This conceptual torus structure is actuated in the synaptic connectivity
279 of the network, with cells on one edge of the sheet connected to those on the
280 opposite side (Figure 2A). When an animal travels continuously in one
281 direction the activity bump moves periodically around the network. Generation
282 of a triangular rather than rectangular organisation of grid fields is dependant
283 on the addition of a phase shift in one axis resulting in a twisted torus attractor
284 manifold (Figure 2A).

285

286 Networks with multiple bumps of activity also have their neurons arranged on
287 a two dimensional manifold, however, a hexagonal population activity bump
288 organisation arises from the most energetically efficient packing of the rings of
289 inhibition; each circle of inhibition repels neighbouring circles to a maximal
290 distance until stabilising into a grid of activity bumps (Figure 2B)(Burak and
291 Fiete, 2009; Couey et al., 2013; Fuhs and Touretzky, 2006). During
292 movement the bumps of activity propagate across the network and individual
293 neurons generate grid firing patterns. Multi-bump networks can either be
294 implemented with periodic boundaries (also referred to as partially periodic
295 networks), so that much as in single bump models the activity bump wraps to
296 the other side of the network. Alternatively, they can have boundaries (also

referred to as aperiodic networks). In this case, when bumps reach the edge of the network they disappear, while on the opposite side of the network local competitive synaptic interactions cause new bumps to spontaneously form as existing bumps move away (Burak and Fiete, 2009; Fuhs and Touretzky, 2006).

When single bump attractors are implemented in E-I networks, each neuron's connections extend over a relatively large fraction of the network (Figure 2A). Thus, neurons making surround connections have their highest connection probability, or connection strength, with neurons at a distance of approximately half the width of the untwisted neural sheet. This distance refers to separation based on the order of connectivity in the network rather than anatomical distance (cf. (Widloski and Fiete, 2014)). Indeed the anatomical organisation of cell bodies of neurons with repeating firing fields appears relatively weak compared to the organisation of neural sheets in continuous attractor network models (Heys et al., 2014), suggesting that synaptic connectivity required for grid firing can be established without ordering of neuronal cell bodies (Widloski and Fiete, 2014). In contrast to single bump networks, the connectivity in multi-bump attractors is much more localised relative to the overall size of the network (Figure 2B). This suggests that quantification of the extent of connectivity between excitatory and inhibitory neurons could be used to distinguish between single and multi-bump models. Local circuit perturbations through thermo- or chemo-modulation in conjunction with multi-unit recordings might also distinguish between single and multi-bump networks (Widloski and Fiete, 2015).

Excitatory-inhibitory interactions provide a common mechanism for grid firing and network oscillations

Successful models of brain circuits should account for network dynamics as well as the firing patterns of individual cells. Dynamics can be modelled by simulating networks of integrate and fire neurons. In these models synaptic input to a neuron charges its membrane capacitance, which is in turn discharged through a resistance. Action potentials occur when the membrane potential crosses a threshold. In exponential integrate and fire neurons the

331 spike threshold has been replaced with an exponential function in order to
332 obtain more realistic spike initiation dynamics (Fourcaud-Trocme et al., 2003).
333 Although integrate and fire models neglect details of morphology and ion
334 channel biophysics, their dynamics are a good approximation for physiological
335 synaptic integration, making them an important bridge between abstract
336 theoretical and more detailed cellular models.

337

338 Models of interacting populations of excitatory and inhibitory exponential
339 integrate and fire neurons can account for both grid firing and gamma
340 oscillations (Pastoll et al. 2013, Solanka et al. 2015). When the models
341 receive theta modulated input the gamma oscillations are nested at a fixed
342 phase within each theta cycle (Figure 4). This is consistent with experimental
343 findings that theta modulated optogenetic activation of layer 2 circuits is
344 sufficient to generate nested gamma activity resembling that observed in
345 behaving animals (Pastoll et al. 2013, Chrobak et al. 2000). In these
346 experiments, and in the corresponding models, gamma oscillations emerge
347 through fast time scale E-I interactions. On each gamma cycle a subset of
348 excitatory neurons fire action potentials. Because the output from each
349 excitatory neurons diverges to many interneurons (Figure 2A), and as each
350 interneuron receives convergent input from many excitatory cells (Figure 2A),
351 this output is sufficient to rapidly trigger action potentials in a large fraction of
352 interneurons. Divergent projections from interneurons send inhibitory
353 feedback to excitatory cells, including those that did not spike. A second
354 gamma cycle is initiated on recovery from this inhibition. The divergent
355 connectivity effectively implements a competitive mechanism that limits the
356 number of excitatory cells active on each theta cycle (Tiesinga and Sejnowski,
357 2009). While E-I models account for both rate coded firing and nested gamma
358 oscillations, a possible limitation of existing models is that theta input is
359 implemented as a common drive to E and I cells. In contrast, only
360 interneurons in the MEC appear to receive inhibitory pacemaker input from
361 the medial septum (Gonzalez-Sulser et al., 2014) while the origin of excitation
362 during theta is currently unknown.

363

364 Models that account for grid firing and nested gamma oscillations exclusively
365 through E-I interactions have been extended to incorporate additional features
366 of MEC circuitry (Solanka et al. 2015). Experimental observations indicate that
367 inhibitory neurons in layer 2 of the MEC may synapse with one another
368 (Pastoll et al. 2013). Addition to E-I models of connections between
369 interneurons stabilises grid firing and increases the frequency of nested
370 gamma oscillations (Solanka et al. 2015). The resulting E-I-I models more
371 easily produce theta oscillations with frequency that matches that of gamma
372 activity in vivo (cf. Chrobak et al. 1998, Colgin et al. 2012). Although E-I
373 models were initially motivated by the indirect connectivity between L2SCs,
374 grid cells are found in deeper layers in which excitatory cells are likely to
375 communicate directly with one another (Dhillon and Jones, 2000). Moreover,
376 while many models for grid firing have focussed on L2SCs, L2PCs also have
377 grid firing fields (Sun et al., 2015), and the synaptic mechanisms through
378 which they interact may differ. When E-I models are extended to include
379 structured connectivity between excitatory neurons in addition to structured E-
380 I interactions they continue to generate grid firing patterns (Widloski and Fiete,
381 2014) and nested gamma oscillations (Solanka et al. 2015). However, when
382 these models were modified further so that inhibitory connectivity is random
383 and only excitatory connectivity is structured they were unable to generate
384 stable grid firing fields (Solanka et al. 2015). We suspect this results from
385 requirements for precise tuning of connections in continuous attractor
386 networks based on structured excitation (cf. (Seung et al., 2000)).

387

388 The strong theta frequency modulation of activity in the MEC raises the
389 question of how attractor states might be maintained during phases of the
390 theta cycle in which activity is suppressed. In principle if activity is suppressed
391 for a sufficient duration then when activity resumes the network has no
392 memory of the location of the previous bump. The spatial representation
393 necessary for path integration is then lost. This loss of bump stability can be
394 prevented by synaptic or intrinsic conductances with slow dynamics
395 (Navratilova et al., 2012; Pastoll et al., 2013; Solanka et al., 2015). For
396 example, on the start of each new theta cycle the residual excitatory NMDA
397 receptor current ensures bumps re-form in their previous location (Figure 4).

398 While there is evidence that NMDA receptors in entorhinal interneurons have
399 sufficiently slow kinetics to perform this role (Jones and Buhl, 1993), it is
400 possible that other biophysical processes that have slow dynamics such as
401 intracellular Ca^{2+} signalling or kinetics of the action potential
402 afterhyperpolarisation could also stabilise attractor states across theta cycles
403 (Navratilova et al., 2012). Alternatively, theta modulation may not completely
404 inactivate entorhinal networks, in which case bump location could be
405 maintained through neurons that remain active across the full theta cycle.
406 Further experimental testing of these ideas will require a better understanding
407 of cellular mechanisms underlying modulation of entorhinal activity during
408 theta states.

409

410 **Noise enables independent control of theta nested gamma oscillations** 411 **and grid firing by modulation of excitatory-inhibitory interactions**

412 Because E-I models account for rate coded grid computation and gamma
413 frequency network activity, they provide an opportunity to investigate
414 relationships between these phenomena. Many cognitive functions, in addition
415 to spatial computation by grid networks, are associated with modulation of
416 gamma activity (Uhlhaas and Singer, 2012). In turn, both cognitive function
417 and gamma activity correlate with changes in E-I interactions. However, the
418 causal relationships between the strength of excitatory and inhibitory
419 synapses, gamma oscillations and computations that might underlie key
420 cognitive functions have been difficult to establish. Systematic investigation of
421 E-I models suggests that these relationships are complex (Solanka et al.
422 2015). First, nested gamma oscillations and grid firing are both promoted by
423 an optimal level of noise within a network. If noise is too low seizure-like
424 states that suppress grid firing tend to emerge, whereas if noise is too high
425 grid fields drift and gamma becomes less coherent. Second, intermediate
426 noise levels maximise the range of excitatory and inhibitory synaptic strengths
427 that support grid firing. Third, gamma activity is a poor predictor of grid firing.
428 Thus, varying the strength of inhibitory or excitatory connections can tune the
429 frequency and power of gamma oscillations without affecting grid firing.
430 Fourth, tuning of intrinsic connections could be used to modulate oscillation-
431 based codes while maintaining grid firing, for example to determine the

432 response of downstream neurons to convergent input from different grid
433 modules. Thus, synchronisation of gamma activity between grid modules
434 might promote, and discordant tuning of gamma between modules might
435 oppose, downstream integration. Therefore, the potential for independent
436 control of gamma oscillations and grid firing, even though both phenomena
437 arise from a common circuit mechanism, has implications for physiological
438 and pathological states of MEC circuits.

439

440

441 **Conclusion**

442 Because multiple abstract models are able to produce grid-like periodic spatial
443 firing patterns, additional experimental constraints are required to establish
444 mechanisms used by the brain to generate grid firing. We have considered
445 evidence that continuous attractor networks that use velocity inputs to
446 compute grid codes for location can be implemented through E-I interactions
447 that are consistent with known properties of microcircuits in the MEC. When
448 implemented with realistic neuronal dynamics these models also account for
449 theta nested gamma oscillations, although so far they are unable to explain
450 theta phase precession in two dimensions without incorporation of additional
451 mechanisms for path integration. Critical future tests of continuous attractor
452 network hypotheses for grid firing include evaluation of predictions for the
453 firing patterns and connectivity of excitatory and inhibitory cell populations. E-I
454 models make further assumptions concerning integration of velocity signals
455 (Pastoll et al. 2013), error correction by place and border input (Guanella et
456 al., 2007; Hardcastle et al., 2015; Pastoll et al., 2013; Sreenivasan and Fiete,
457 2011) and sources of tonic drive (Bonnevie et al., 2013; Burak and Fiete,
458 2009; Pastoll et al., 2013) that we have not considered here. Experimental
459 evidence for how these signals are integrated by MEC circuits will further
460 constrain possible models. Progress in establishing experimentally
461 constrained models for spatial representation by cell populations in the MEC
462 may serve as a proof of principle for understanding cellular and synaptic
463 mechanisms for high-level computations by cortical circuits in general.

464

465

466

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615 **Additional information**

616

617 Competing interests

618 None of the authors has any conflicts of interest.

619

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627

628 **Figure 1. Components of a generic E-I model for generation of grid firing**
629 **and nested gamma oscillations**

630 Integration of velocity input by continuous attractor networks built from
631 interacting excitatory and inhibitory neurons can generate grid firing fields.
632 When the networks receive a theta modulated input they generate gamma
633 frequency output that is modulated at theta frequency. A spatial input is
634 required to oppose drift in the grid representation. Data are from Pastoll et al.
635 (2013).

636

637

638 **Figure 2. Single and multi-bump attractor model of grid firing have**
639 **distinct circuit organisation**

640 In single bump models grid firing of excitatory cells can be generated by
641 synaptic profiles that produce either surround excitation or surround inhibition.
642 The surround connectivity is strongest for connections to neurons at a
643 distance of about one half the width of the sheet. Each neuron makes
644 divergent connections to many target neurons, and receives convergent input
645 from many pre-synaptic neurons. In multi-bump networks the strongest
646 connections are onto neurons at a much shorter distance relative to the size
647 of the sheet. The upper graphs plot synaptic strength as a function of position
648 in the neural sheet, which is given a width of one. The plots below schematise
649 the resulting E-I connectivity, illustrate the organisation of activity in the neural
650 sheet and the organisation of excitatory cell activity in three dimensions. The
651 connectivity profiles shown for the multi-bump models are based on networks
652 containing only inhibitory neurons, with either surround inhibition (Burak and
653 Fiete, 2009) or local inhibition (Couey et al., 2013). The networks could be
654 considered as having dedicated interneurons receiving input from each
655 excitatory neuron.

656

657

658 **Figure 3. Spatial firing of interneurons in E-I attractor models**

659 (A) Schematic organisation of an E-I network with additional random place
660 field inputs to each interneuron (left). Example firing fields of I cells (middle)
661 and E cells (right) are shown adjacent to the schematised neurons. (B)

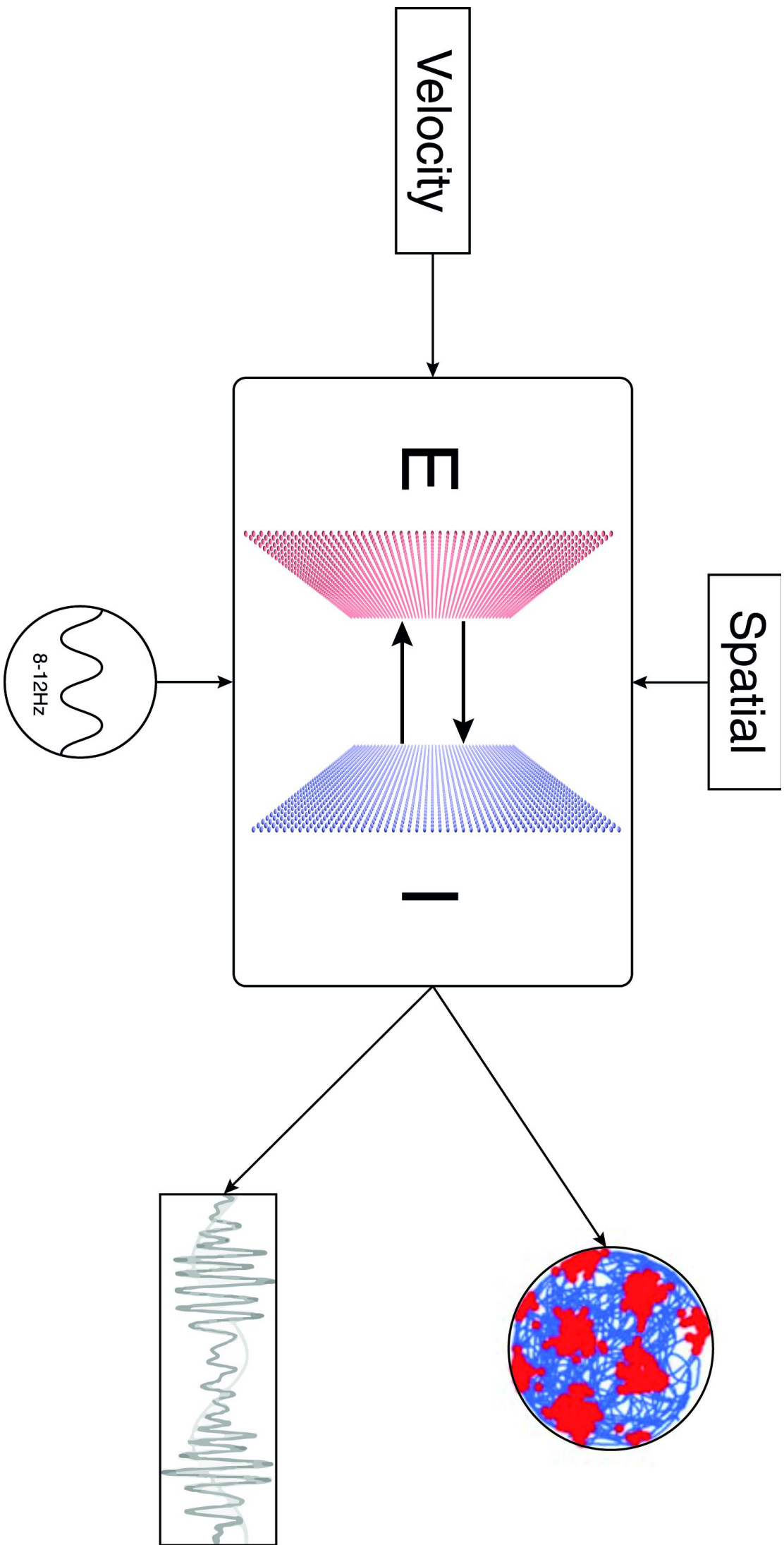
662 Histograms of the spatial sparsity (upper) and gridness score (lower) for E-I
663 networks simulated as in (A). Note that most interneurons and many
664 excitatory cells have grid scores < 0.5 . Data are from Solanka et al. 2015

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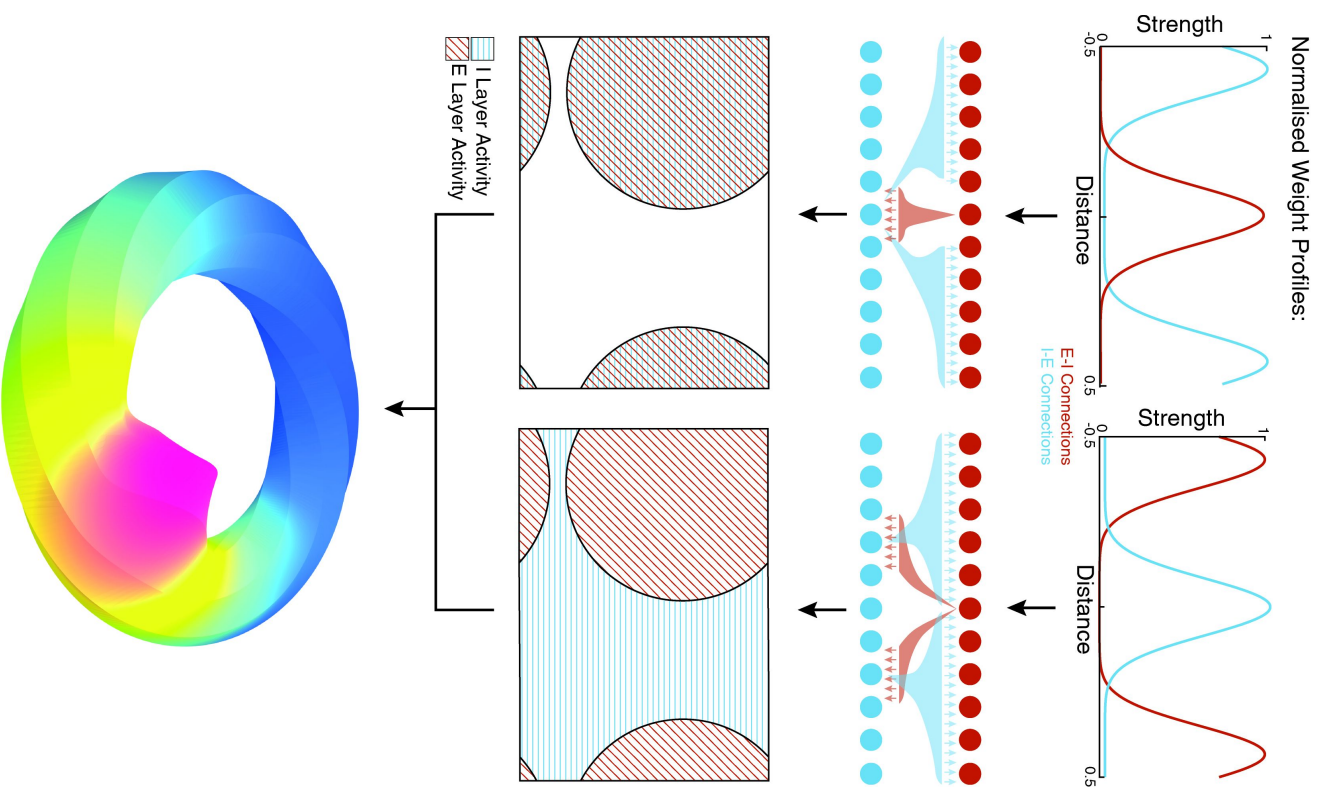
667 **Figure 4. Theta nested gamma activity in E-I models**

668 Spike rasters for E cells (red) and I cells (blue) during two theta cycles (grey).
669 The excitatory synaptic input to a representative I cell is illustrated below.
670 Note that a substantial residual inward current (blue shading) is maintained
671 during the phase of the theta oscillation when spike activity of excitatory cells
672 is reduced. The residual current enables the bump of activity to be maintained
673 across theta cycles. Data are from Pastoll et al. (2013) and Solanka et al.
674 (2015).



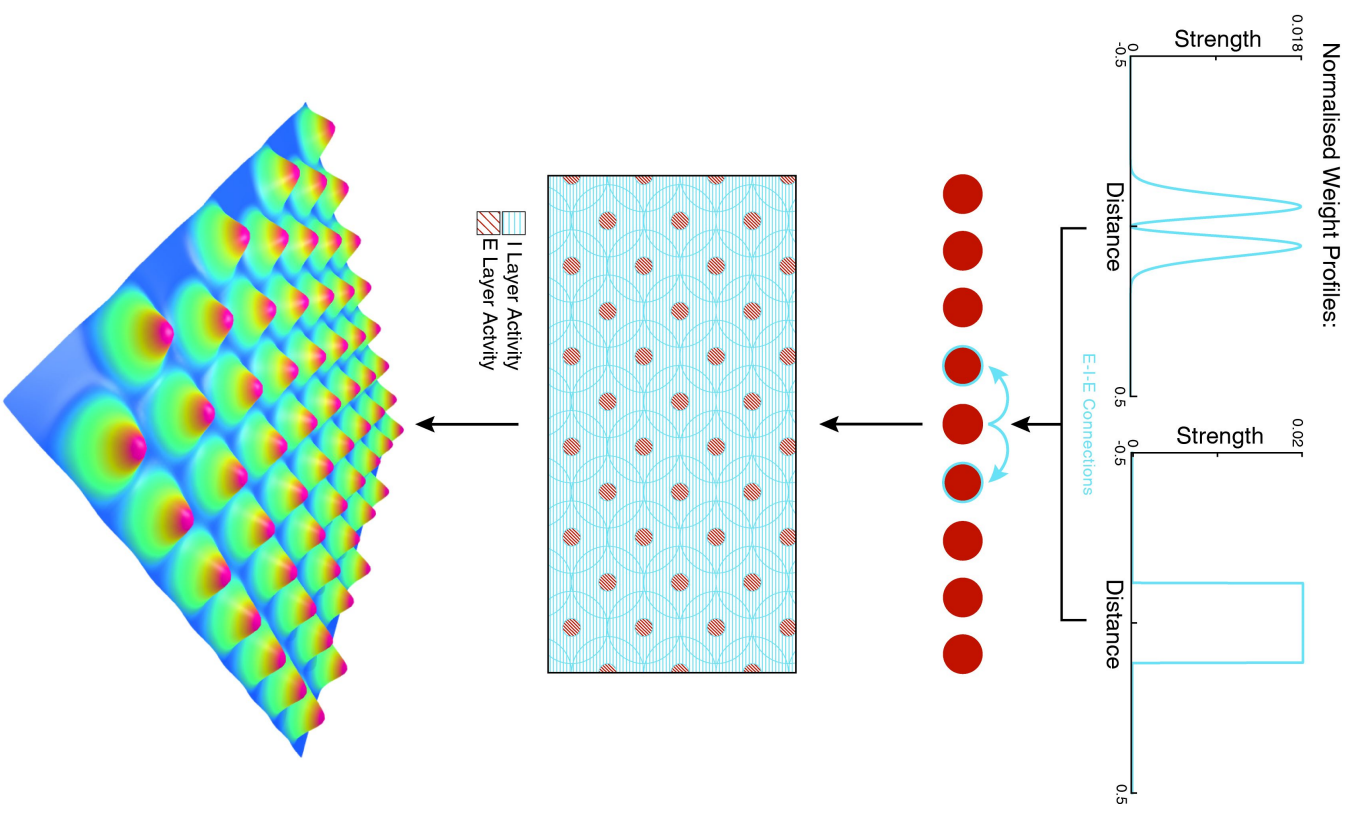
A

Single Bump

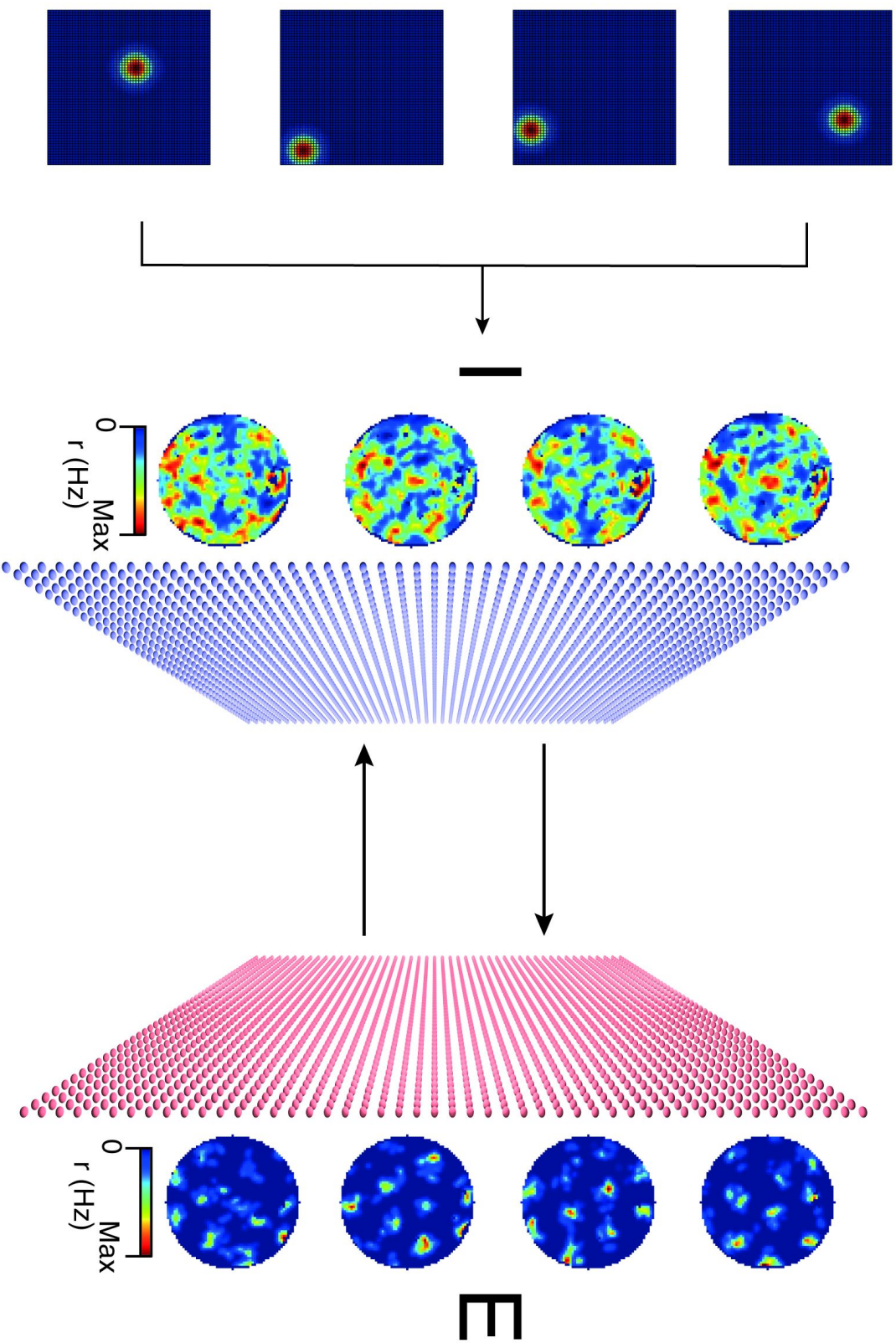


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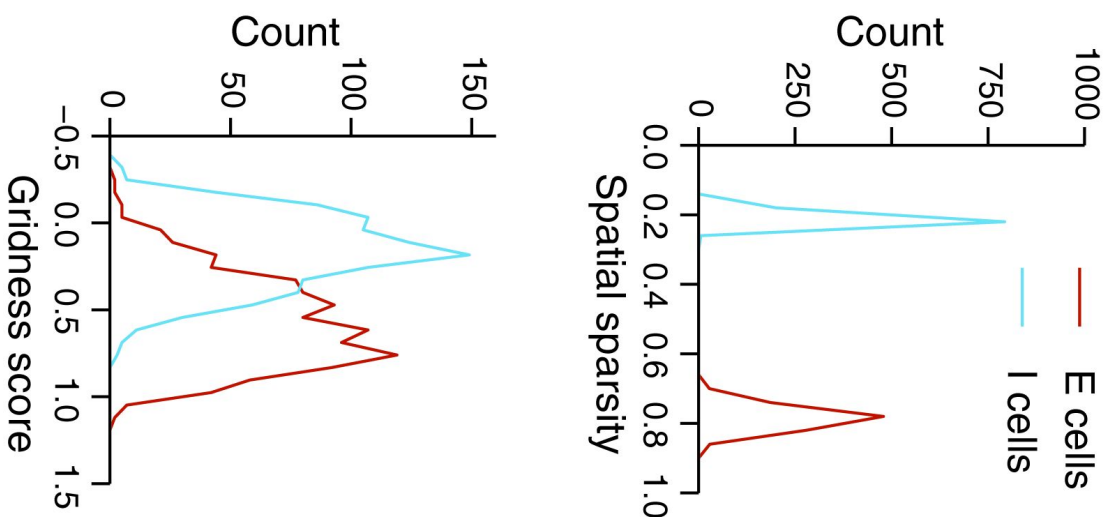
Multi-Bump



A



B



Theta
Envelope

Excitatory Cell
Spikes

Inhibitory Cell
Spikes

0

Interneuron
Membrane
Current

-200

-400

-600

